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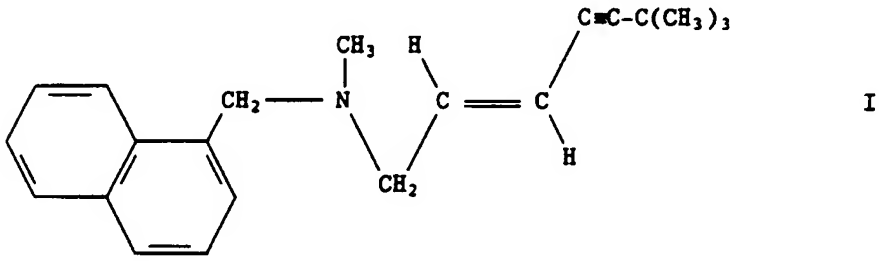
(54) **Pharmaceutical composition containing terbinafine as an anti-mycotic agent.**

(57) The invention concerns topical formulations such as nail varnishes comprising as the active agent the compound of formula I



I

in free base form or in acid addition salt form,
together with a polymeric film former and further excipients as appropriate. It also concerns a process of preparation of such preparations by mixing with an appropriate polymeric film former and conventional further excipients as appropriate, and a method of treatment of onychomycosis.

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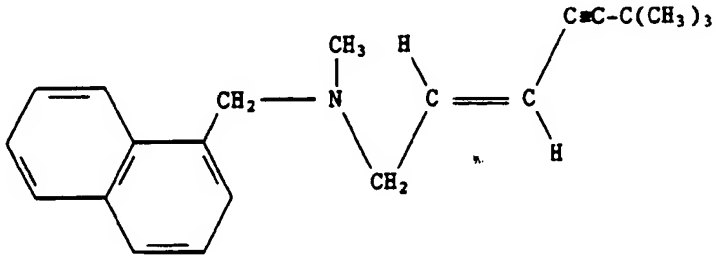
The present invention relates to topical formulations containing an allylamine compound as the pharmacologically active agent.

It concerns a topical formulation such as a a nail varnish comprising as the active agent the compound of formula I



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in free base form or in acid addition salt form,
together with a polymeric film former such as polyvinyl acetate, acrylic- and methacrylic-acid alkyl ester copolymerisates with quaternary ammonium groups or methylvinylether-maleic acid monoalkyl ester copolymerisates and further excipients as appropriate.

The compound of formula I may be in free base form or in acid addition salt form. An acid addition salt form may be prepared from the free base form in conventional manner and vice-versa. Examples of suitable acid addition salt forms are the hydrochloride, the lactate and the ascorbate. The free base and the hydrochloride are preferred.

The compound of formula I is known from e.g. EP-A-24587. It belongs to the class of allylamine antimycotics. It is known in the art under its generic name as terbinafine, and it is commercially available under the trademark LAMISIL. Apart from its efficacy against dermatophytes after oral as well as topical administration, we have found, it is also highly efficient after oral application in the treatment of onychomycosis, as it has a strong fungicidal activity and high affinity to the keratin of the nails, where it is enriched. Therefore a significantly higher cure rate may be achieved than with conventional therapies such as e.g. oral treatment with griseofulvin.

Although the compound of formula I is a very safe drug, systemic treatment of onychomycosis offers some disadvantages, e.g. exposure of the whole organism to the drug substance and the need for rather high doses. Therefore the possibility of local, namely topical treatment is highly desirable and would be preferred by many patients. On the other hand many attempts have been made with various drugs, e.g. griseofulvin, to prepare topical formulations for the treatment of onychomycosis but the results obtained were unconvincing. This might be related to insufficient penetration of the drugs into the deeper layers of the nails.

It has now been found that the compound of formula I, when it is formulated in the proper vehicle, is surprisingly highly efficient upon topical application to infected nails in the treatment of onychomycosis .

Such formulations should ideally have the following properties:

- As penetration into the infected nails is a rather slow process, they should build up a depot after application from where the drug can freely diffuse into the nail tissue;
- they should have the capacity to easily release the drug;
- they should be comfortable for the patient, e.g. easy to apply, to be applied with low frequency, easy to remove and well tolerated.

It has been found that such formulations can be obtained with the benefits mentioned above and a high efficacy by formulating the compound of formula I in free base form or in acid addition salt form as a nail varnish containing one or more suitable film formers and conventional further excipients as appropriate.

Components of the nail varnishes of the invention are:

1. The compound of formula I in free base form or in acid addition salt form.
2. A polymeric film former. This may be either water-soluble or water-insoluble. Polymers suitable as water-insoluble film formers are e.g. polyvinylacetate, acrylic- and methacrylic-acid alkyl ester copolymerisates with quaternary ammonium groups and methylvinylether-maleic acid monoalkyl ester copolymerisates. Whereas the polymer most frequently used in nail varnishes is nitrocellulose, this polymer cannot be used in the present invention due to chemical incompatibility with the drug substance. Polymers suitable as water-soluble film formers are in particular polymers solubl in water as well as in organic solvents. Such polymers are .g. polyvinylpyrrolidone (PVP) and vinylpyrrolidone-vinyl acetate copolymers. Preferably the mean molecular weight of these copolymers is about 60.000 ± 15.000. A commercially available polymer

of the latter class is e.g. known under the tradename KOLLIDON VA 64. Preferred are water-insoluble film formers such as polyvinyl acetate or acrylic- and methacrylic-acid alkyl ester copolymerisates with quaternary ammonium groups as e.g. availabl under the tradenames EUDRAGIT RL and EUDRAGIT RS resins or methylvinyleth r-maleic acid monoalkyl ester copolymerisates as .g. available under the tradename GANTREZ ES.

The compound of formula I and the polymeric film former are preferably present in the composition in the proportion of from about 1 : 0.5 to about 1 : 25, more preferably of from about 1 : 1 to about 1 : 20 and most preferably of from about 1 : 1 to about 1 : 10 on a w/w basis.

The compound of formula I makes up from e.g. about 0.5 % to about 30 %, preferably from about 1 % to about 20 % of the total composition on a weight basis.

In addition to the drug substance and the polymeric film former the compositions normally contain conventional further excipients, e.g. a solvent system. This can be either aqueous or organic or a mixture between organic solvents and water. Organic solvents are those which are physiologically acceptable and compatible with the drug substance and the further ingredients of the composition. Typical solvents are ethanol, isopropanol, acetone and ethyl acetate. The preferred solvent system is ethanol, with the addition of a certain amount of water. The amount of water is in most cases less than the amount of the solvents. Typical water/solvent ratios are e.g. below 1 : 3. However in some cases the amount of water may exceed that of the solvent. It may then be e.g. up to 2.5 : 1.

The compositions of the invention usually also contain additional ingredients which stabilize the formulations and improve their properties. In particular such further excipients are:

- plasticizers such as dialkylphthalates, e.g. dibutylphthalate, hydroxy-fatty acid oils, e.g. castor oil, triglycerides and silicon oils ;
- film modifiers which change the properties of the main film former, in particular improve its application properties, e.g. hardness after evaporation of the solvent or flexibility on the nail. These modifiers can be e.g. acrylic ester resins,
arylsulfonamide-formaldehyde resins, cellulose derivatives or polyamide resins;
- surfactants, e.g. polyethylenglycol-alkylethers (e.g. as available under tradename BRIJ), which help solubilize the drug especially in vehicles containing water;
- penetration enhancers, e.g. azole, dimethylsulfoxide, unsaturated fatty alcohols, surfactants and propylene glycol;
- colouring agents;
- antioxidants, e.g. tocopherol;
- complexing agents, e.g. ethylendiamintetracetic acid (Komplexon III); and
- UV-absorbers.

The topical formulations of the invention such as nail varnishes can be obtained by a process comprising mixing the compound of formula I in free base form or in acid addition salt form with an appropriate polymeric film former such as polyvinyl acetate or acrylic- and methacrylic-acid alkyl ester copolymerisates with quaternary ammonium groups or methylvinylether-maleic acid monoalkyl ester copolymerisates and further excipients, e.g. the solvent system, as appropriate. The process of the invention may be effected in conventional manner.

The compositions according to the invention are especially useful for the treatment of onychomycosis. An indicated daily dose to be administered typically is from about 0.05 to about 5.0 mg of the compound of formula I per square centimeter of the treated nail material. Preferred application rates are from about 0.1 to 3.0 mg per square centimeter. The concentration of the compound of formula I in the tissue at the place of action is preferably e.g. between 0.001 and 1.0 mg/g depending on the type of fungal nail infection and type of treated nails. Applications may take place once a day in severe cases or even only once a week. Preferably treatments are repeated every second or third day.

Both the nail material at fingers and toes may be treated when infected with fungi causing onychomycosis, e.g. dermatophytes, yeast fungi or molds.

The following examples illustrate the invention (the compound of formula I is herein briefly named compound 1):

Example 1: Nail varnish 20 %

Ingredient	Amount (g/ 100 g)
Compound 1 in free base form	20.00
Dibutyl phtalate	0.70
Acrylic resin, hard durable (e.g. PARALOID A-21)	2.50
Polyvinyl acetate	13.50
Ethyl acetate	63.30

Example 2: Nail varnish 5 %

Ingredient	Amount (g/100 g)
Compound 1 in free base form	5.0
Dibutyl phthalate	0.6
50 % solution of a copolymerisate of methyl-vinylether and maleic acid monobutyl ester in ethanol (e.g. GANTREZ ES 425)	30.0
Ethanol	30.0
Ethyl acetate	34.4

Example 3: Nail varnish 5%

Ingredient	Amount (g /100 g)
Compound 1 in free base form	5.0
Glycerol triacetate	2.0
Oleic alcohol	2.0
50 % solution of a copolymerisate of methyl-vinyl-ether and maleic acid mono-ethyl ester in ethanol (e.g. GANTREZ ES 225)	40.0
Water	10.0
Ethanol 94 % W/W	40.98
Butyl hydroxytoluene	0.02

Exampl 4: Nail varnish 5 %

Ingredients	Amount (g / 100 g)
Compound 1 in hydrochloride form	5.0
Glycerol triacetate	2.0
Isopropyl myristate	2.0
GANTREZ ES 225	40.0
Water	10.0
Ethanol 94 % W/W	40.98
Butyl hydroxytoluene	0.02

Example 5: Nail varnish 5 %

Ingredients	Amount (g / 100 g)
Compound 1 in hydrochloride form	5.0
Glycerol triacetate	2.0
Isopropyl myristate	2.0
copolymerisate of acrylic- and methacrylic-acid esters with a small amount of quaternary ammonium groups (e.g. EUDRAGIT RL 100)	20.0
Acrylic resin, hard durable (e.g. PARALOID B-82)	2.5
Water	5.0
Ethanol 94 % W/W	63.48
Butyl hydroxytoluene	0.02

Example 6: Nail varnish 2 %

Ingredients	Amount (g / 100 g)
Compound 1 in hydrochloride form	2.0
Castor oil	3.0
50 % solution of a copolymerisable of methyl-vinylether and maleic acid mono-butyl ester in ethanol (e.g. GANTREZ ES 425)	40.0
Ethanol 94 % W/W	55.0

Example 7: Nail varnish 10% - water removable

Ingredient	Amount (g/100 g)
Compound 1 in hydrocvhloride form	10.0
Isopropyl myristate	6.0
Vinylpyrrolidone-vinylacetate-copolymer	12.0
Water	5.0
Isopropanol	67.0

Example 8: Nail varnish 5 % - water removable

Ingredient	Amount (g/100 g)
Compound 1 in hydrochloride form	5.0
Isopropyl myristate	6.0
Vinylpyrrolidone-vinylacetate-copolymer	10.0
Isopropanol	79.0

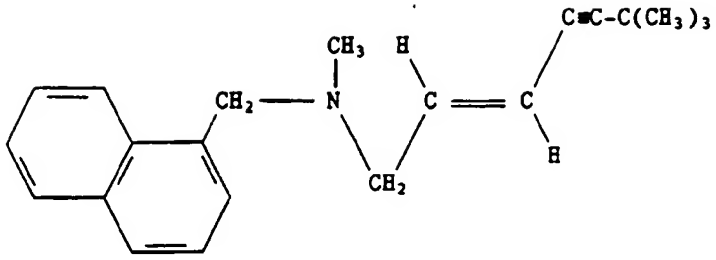
Example 9: Nail solution 1 % - aqueous - water removable

Ingredient	Amount (g/100 g)
Compound 1 in hydrochloride form	1.0
Polyoxyethylene-4-lauric alcohol (e.g. BRIJ 30)	2.0
Vinylpyrrolidon-vinylacetate-copolymer	12.0
1,2-Propylene glycol	5.0
Ethanol 94 % W/W	25.0
Sodium pyrosulfite	0.1
Na-EDTA	0.1
Distilled water	54.8

The efficacy of the formulations of the invention can be shown in vitro or in vivo. A suitable in vitro method is measurement of the penetration through excised nails where it can be shown that fungicidally effective concentrations of the drug are reached also in deeper layers of the nail tissue. A further in vitro method is the measurement of the dissolution rate of the drug from a dried varnish layer where it can be shown that fungicidally effective amounts of the drug are sufficiently released from dried varnish layers. In vivo the most convincing test is the double blind study with onychomycosis.

Claims

1. A topical formulation such as a nail varnish for the treatment of onychomycosis comprising as the active agent the compound of formula I



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together with a polymeric film former such as polyvinyl acetate or acrylic- and methacrylic-acid alkyl ester copolymerisates with quaternary ammonium groups or methylvinylether-maleic acid monoalkyl ester copolymerisates, and further excipients as appropriate.

2. A formulation according to claim 1 wherein the polymeric film former is polyvinyl acetate.

3. A formulation according to claim 2 wherein the polymeric film former is an acrylic- and methacrylic- acid alkyl ester copolymerisate with quaternary ammonium groups.

4. A formulation according to claim 1, wherein the polymeric film former is a methylvinylether-maleic acid monoalkyl ester copolymerisate.

5. A formulation according to any one of claims 1 to 4 wherein the mixture ratio of the compound of formula I and the polymeric film former is from about 1:0.5 to about 1:25 on a w/w basis.

6. A formulation according to claim 5, wherein the mixture ratio of the compound of formula I and the polymeric film former is from about 1 : 1 to about 1 : 20.

7. A formulation according to claim 6, wherein the mixture ratio of the compound of formula I and the polymeric film former is from about 1 : 1 to about 1 : 10.

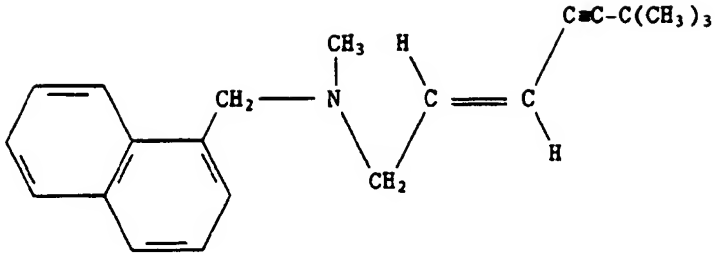
8. A formulation according to any one of claims 1 to 4 wherein the compound of formula I is present from about 0.5% to about 30% of the total composition on a w/w basis.

9. A formulation according to claim 8 wherein the compound of formula I is present from about 1% to about 20% of the total composition.

10. A process for the preparation of a topical formulation such as a nail varnish according to claim 1 comprising mixing the compound of formula I as defined in claim 1 in free base form or in acid addition salt form with an appropriate polymeric film former such as polyvinyl acetate or acrylic- and methacrylic-acid alkyl ester copolymerisates with quaternary ammonium groups or methylvinylether-maleic acid monoalkyl ester copolymerisates, and conventional further excipients as appropriate.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of a topical formulation such as a nail varnish for the treatment of onychomycosis comprising as the active agent the compound of formula I



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in free base form or in acid addition salt form,
together with a polymeric film former such as polyvinyl acetate or acrylic- and methacrylic-acid alkyl ester copolymerisates with quaternary ammonium groups or methylvinylether-maleic acid monoalkyl ester copolymerisates, and further excipients as appropriate, comprising mixing the compound of formula I in free base form or in acid addition salt form with an appropriate polymeric film former such as polyvinyl acetate or acrylic- and methacrylic-acid alkyl ester copolymerisates with quaternary ammonium groups or methylvinylether-maleic acid monoalkyl ester copolymerisates, and conventional further excipients as appropriate.

2. A process according to claim 1 wherein the polymeric film former is polyvinyl acetate.

3. A process according to claim 2 wherein the polymeric film former is an acrylic- and methacrylic- acid alkyl ester copolymerisate with quaternary ammonium groups.

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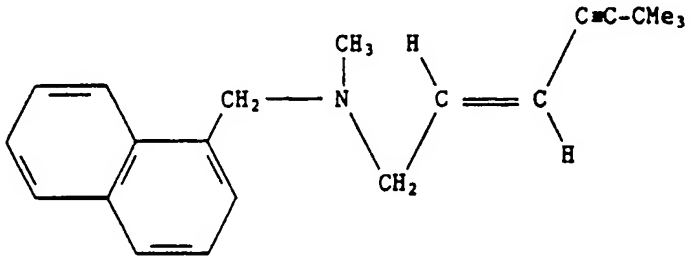

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EUROPEAN SEARCH REPORT

Application Number
EP 92 81 0380

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
E	EP-A-0 503 988 (L'OREAL) * abstract *	1-10	A61K7/043 A61K31/135
Y	WO-A-8 702 580 (DERMATOLOGICAL PRODUCTS OF TEXAS) * abstract; claims 11-13 *	1-10	
Y	WO-A-8 806 884 (LENGYELNE H. ET AL.) * abstract *	1-10	
Y	EP-A-0 226 984 (HOECHST) * abstract *	1-10	
Y	EP-A-0 399 858 (L'OREAL) * abstract *	1-10	
Y	GB-A-2 197 194 (MERCK & CO) * abstract *	1-10	
A	EP-A-0 298 271 (HOECHST) * page 3, line 33 *	2	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A	EP-A-0 389 778 (F.HOFFMANN-LA ROCHE) * abstract *	3	A61K
A	FR-A-2 397 186 (MALLINCKRODT) * page 1, line 1 - line 5 *	4	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	01 FEBRUARY 1993	AVEDIKIAN P.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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L : document cited for other reasons

& : member of the same patent family, corresponding document

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